REMARKS

Claims 1 and 8-13 are currently pending. These claims have not been amended. Claims 14-22, previously indicated as withdrawn by the Examiner, have been cancelled. Applicants reserve the right to file cancelled subject matter in divisional or continuation applications.

Applicants respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Rejection under 35 U.S.C. § 103(a)

Claims 1 and 8-13 are rejected for allegedly being unpatentable over Kleiber et al. (J. Molecular Diagnosis, 2(3): 158-166, (2000)), Kawai et al. (J. Medical Virology, 58: 121-126, (1999)), Resnick et al. (USP 5,527,669), Michinori et al. (JP 103899), Sherer et al. (Nucleic Acids Research, 5: 3141-3156, (1978)), and Lee et al. (USP 6,316,610). Applicants respectfully assert that a *prima facie* case of obviousness has not been established because none of the above cited references, taken singly or in combination, teach or suggest all of the recited limitations of the presently claimed invention.

A. The Claimed Subject Matter

Claim 1 is directed to a method of detecting the presence of HCV nucleic acids in a test sample by (a) reverse transcribing and amplifying HCV in the test sample with a pair of primers corresponding to SEQ ID NOs: 1 and 2; (b) hybridizing the amplified HCV nucleic acid with a labeled probe having a nucleotide sequence consisting of SEQ ID NO: 3 in the presence of an enzyme that cleaves the labeled probe when it hybridizes to the amplified HCV nucleic acid; and (c) detecting the label.

B. The Cited References

Kleiber et al. teaches a reverse transcription-PCR assay for quantifying HCV RNA using the TaqMan principle. As admitted by the Examiner, Kleiber et al. does not teach any of the following:

(1) does not teach the HCV primer corresponding to SEQ ID NOs: 1;

PAGE 13/33 * RCVD AT 11/4/2004 1:07:19 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/2 * DNIS:8729306 * CSID: * DURATION (mm-ss):10-16

(2) does not teach the HCV primer corresponding to SEQ ID NOs: 2;

(3) does not teach the probe corresponding to SEQ ID NO: 3; or

(4) does not teach a probe containing VIC or TAMRA as the label.

Furthermore, with respect to claim 9, Kleiber et al. does not teach introducing lambda phage-HCV nucleic acids to a test sample. Instead, Kleiber et al. teaches adding an internal control probe that has primer regions that are identical to HCV (see Kleiber at page 159, paragraph 2).

To make up for the many deficiencies in the primary reference, the Examiner attempts to pick and chose the missing elements from other references using the claimed invention as a guide. The Examiner turns to Kawai for the teaching of a probe that uses FAM and TAMRA as the Taqman probe labels, just one of the labels recited in claim 8. The Examiner turns to Resnick et al. for the HCV amplification primers corresponding to SEQ ID NOs: 1 and 2. However, Resnick et al. is not a TaqMan assay.

The Examiner goes to Michinori et al. (11-103899) allegedly for a probe that is the same for SEQ ID NO:3. Office Action 5/4/2004, page 3. However, the probe of Michinori et al. does not read on SEQ ID NO: 3 as presently claimed. [step (b) of claim 1 is directed to "an oligonucleotide probe consisting of the sequence set forth in SEQ ID NO: 3" and not a probe comprising SEQ ID NO: 3] . Furthermore, Michinori's assay involves standard PCR, not the Taqman format. (As discussed by Dr. Lewinski, ahead, the probe and primer requirements for a Taqman assay are more stringent than for standard PCR.)

The Examiner goes to Scherer et al. for the genomic structure and sequence of lambda phage. However, Scherer does not teach a lambda phage-HCV nucleic acid hybrid as recited in claim 9. Finally, the Examiner goes to Lee et al. for methods of conjugating fluorescent and quencher dyes, such as VIC and FAM to oligonucleotides.

"To establish a *prima facie case* of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to

PAGE 14/33 * RCVD AT 11/4/2004 1:07:19 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/2 * DNIS:8729306 * CSID: * DURATION (mm-ss):10-16 .

combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations" (MPEP 2143).

Applicants respectfully submit that none of the three criteria for a *prima facie* rejection has been met by the current rejection. There is no suggestion or motivation to combine the teachings of these various references. First, neither Kleiber et al. nor Kawai et al., both references which teach a reverse transcription-PCR assay for quantifying HCV RNA using the TaqMan principle, provide any suggestion or motivation to use the primer sequences taught in Resnick et al., which does not employ the TaqMan approach.

Secondly, neither Kleiber et al. nor Kawai et al. provide any suggestion or motivation to use an oligonucleotide probe consisting of SEQ ID NO: 3. In fact, Michinori et al. nor any of the other references discloses an oligonucleotide probe consisting of SEQ ID NO: 3. Furthermore, none of the cited references, including Sherer et al., provide any suggestion or motivation to introduce lambda phage-HCV nucleic acid hybrids as recited in claim 9.

The failure of any reference to teach an oligonucleotide probe consisting of the sequence set forth in SEQ ID NO: 3, as is recited in claim 1 indicates that the rejection has failed to teach or suggest all of the claim limitations, a requirement for an obviousness rejection. The same applies to claim 8 as no reference teaches introducing lambda phage-HCV nucleic acid hybrids. Clearly, no *prima facie* rejection has been stated.

With respect to motivation to combine and expectation of success, two tests that must be established for a *prima facie* obviousness rejection, the present rejection rests on the Examiner's unsubstantiated personal opinion that because the entire nucleotide sequence of HCV is known, it would be *prima facie* obvious to generate an HCV assay with any particular primer or probe sequence combination.

This may be a convenient way of dispensing with a case but it's not the law. The Examiner must rely on something other that personal opinion. Furthermore, this view that any nucleic acid can be used because the sequence of HCV is known is inconsistent with the art and the experience of one of ordinary skill in the art as demonstrated by the attached declaration of

PAGE 15/33 * RCVD AT 11/4/2004 1:07:19 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/2 * DNIS:8729306 * CSID: * DURATION (mm-ss):10-16

Dr. Michael Lewinski, an inventor of the instant application and an expert in DNA based nucleic acid diagnostic assays for infectious agents. Dr. Lewinski concludes from his own experience and from others who have published in the field that the quality of a nucleic acid based assay is very much dependent on the particular primers and probe sequences chosen.

Dr. Lewinski discusses a publication by Wang et al., *BioTechniques* 17: 82-87 (1994) (already of record), which teaches the importance of particular primer pairs in the sensitivity of detecting target nucleic acids in PCR. According to Dr. Lewinski, Wang et al. teaches that primers that differ even "slightly" in position can exhibit 100- to 1000-fold differences in amplification sensitivity. Wang et al. describes dramatic differences in sensitivity using different primer combinations. As stated by Wang et al.:

> Our results suggest that primers are decisive for the sensitivity of PCR, and that there is **no reliable means to predict the sensitivity achieved by a given primer pair.** Some primer pairs, which have been designed taking into account the basic rules, **do not work** as efficiently as expected. **An extensive search** for optimal reaction protocol **may be unfruitful** with these primers.

Wang et al., page 85, paragraph 5 (emphasis added in bold). As discussed by Dr. Lewinski, the experiences of Wang et al. are not unusual.

Dr. Lewinski concludes that there are no reliable means to predict which primer pairs can be successfully employed in the detection of a given target nucleic acid. Its stands, therefore, that because there are no reasons which can explain the difference in sensitivity between primer pairs, there can be no reasonable expectation of success when combining the primers and probes from different prior art references.

Furthermore, it must be considered that the TaqMan amplification assay, which the present claims cover, are more complex than standard PCR assays. According to Dr. Lewinski, the primers and the probe in the TaqMan format must be able to function together at the same time since the probe must bind to amplified product as it is extended from the primers. In contrast, the probe in a standard PCR assay is applied after the PCR has been completed and amplicons generated. Also according to Dr. Lewinski, primers pairs and probes that might work

PAGE 16/33 * RCVD AT 11/4/2004 1:07:19 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/2 * DNIS:8729306 * CSID: * DURATION (mm-ss):10-16

acceptably in standard PCR might fail or perform poorly in the TaqMan format. Dr. Lewinski concludes that one of ordinary skill would not have had a reasonable expectation of success for combining the probes of Resnick et al. and the probe of Michinori et al. both from standard PCR assays to be used in a TaqMan style PCR assay as described in Kleiber et al.

Thus, the Examiner's unsupported personal opinion that any primer and probe could be obtained because the HCV sequence was known is legally insufficient to support a *prima facie* obviousness rejection and is contrary to the facts as demonstrated by Dr. Lewinski, an expert in the filed of infectious disease nucleic acid assays.

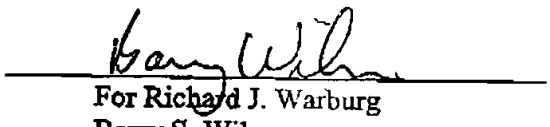
Because no *prima facie* case of obviousness has been established, or, in the alternative, any *prima facie* case of obviousness that may have been established has been rebutted, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn or reversed.

CONCLUSION

In view of the foregoing remarks and amendments submitted herein, Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the address and telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,

Date November 4, 2004



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PAGE 17/33 * RCVD AT 11/4/2004 1:07:19 PM [Eastern Standard Time] * SVR:USPTO-EFXRF-1/2 * DNIS:8729306 * CSID: * DURATION (mm-ss):10-16